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In reply, please refer to:
File:

December 11, 2001

Anthrax Update

Dear Health Care Provider:

As of December 11, 2001 there have been 22 cases of intentional anthrax diagnosed in the United States. There have been 11 cases of inhalational anthrax and 11 cases of cutaneous anthrax. The two initial reports were from persons who worked at the AMI Building in Boca Raton, Florida. Additional cases have been reported from New York City, New Jersey, Connecticut, and the Washington, D.C. metropolitan area. All but two cases have been epidemiologically linked to anthrax spores sent through the mail. The source of exposure in two cases remains unknown, although cross-contamination with mail that may have been sent through a Trenton, New Jersey post office is suspected. No new anthrax cases have been reported in the United States since November 14, 2001.

Since September 11, 2001, there have been no confirmed cases of anthrax reported to the Hawaii Department of Health. The State Laboratories Division has examined over 400 specimens and has found no evidence of environmental anthrax spores. The main U.S. Post Office in Honolulu underwent extensive environmental testing for anthrax in November, and all tests were negative.

All health care providers must remain alert to the possibility of additional bioterrorist attacks including the possibility of new anthrax cases. Health care providers are urged to include anthrax in the differential diagnosis for patients presenting with:

- An ulcerative or necrotic skin lesion (especially if painless and associated with surrounding edema and/or a blackened eschar),
- Unexplained respiratory distress or sepsis (especially if associated with mediastinal widening on radiographic studies),
- Microbiologic findings of a Gram positive rod or Bacillus species from a sterile site (blood, cerebrospinal fluid, or pleural fluid).

Cutaneous Anthrax

The diagnosis of cutaneous anthrax is based upon the typical appearance and progression of the skin lesion, and confirmatory microbiology tests. Gram stain and culture of the skin lesion can isolate *Bacillus anthracis*. Blood cultures may be positive for *B. anthracis*. Consider skin biopsy if the patient is on antimicrobials or if Gram stain and culture are negative for *B. anthracis* and clinical suspicion remains high. Immunohistochemical stains or polymerase chain reaction testing for the presence of *B. anthracis* can be performed on the skin biopsy specimen. Because patients with cutaneous anthrax in this outbreak may have also been exposed to aerosolized anthrax spores, the total duration of treatment is 60 days rather than the standard 7 to 10 days of therapy.

Inhalational Anthrax

Ten of the 11 recent cases of inhalational anthrax on the mainland had abnormal chest x-rays on initial presentation. Chest x-ray abnormalities included mediastinal widening, paratracheal and hilar fullness, pleural effusions, and pulmonary infiltrates. Pulmonary infiltrates or effusions were initially seen in two cases without evidence of mediastinal widening. Chest computed tomography was helpful in further characterizing abnormalities in the lungs and mediastinum and was more sensitive than chest x-ray in revealing mediastinal lymphadenopathy. Hemorrhagic pleural effusions often requiring chest tube drainage were common. Blood cultures were positive for all that had not previously received antibiotics. Positive blood culture results were available within 18 to 24 hours after specimens were obtained.

The diagnosis of anthrax was established in three patients without growth of *B. anthracis* from clinical specimens. Immunohistochemical staining of pleural fluid, pleural or transbronchial biopsy specimens for *B. anthracis*-specific cell wall and capsular antibodies confirmed the diagnosis in three cases. *B. anthracis* DNA was also identified by polymerase chain reaction tests on pleural fluid or blood. Serology tests from one patient demonstrated a > 4-fold increase in levels of serum antibody (IgG) to the protective antigen component of anthrax toxin. Autopsies of all fatal cases demonstrated hemorrhagic mediastinal lymphadenitis and disseminated *B. anthracis* infection.

Patients sought care a median of 3.5 days (range 1 to 7 days) after onset of symptoms. Eight of 11 patients were in the initial phase of illness when they first sought care. Of these eight, six received antibiotics with activity against *B. anthracis* on the first day of care, and all six survived.

Treatment

Treatment recommendations for anthrax remain the same as stated in the October 18, 2001 State of Hawaii Department of Health Anthrax Alert (available on the Department of Health website at *http://www.state.hi.us/doh/anthrax/index2.html*) with the following clarifications:

1. For inhalational anthrax, anthrax meningitis, and extensive or bacteremic cutaneous anthrax, at least two intravenous antibiotics effective against *B. anthracis* are recommended for initial therapy.

2. Centers for Disease Control (CDC) Recommendations – October 26, 2001

   - **CDC recommends ciprofloxacin or doxycycline** as part of initial therapy of inhalational or cutaneous anthrax. **They also state that combination therapy with two or more antimicrobials may be appropriate in patients with severe infection.** The CDC believes that the use of penicillin or amoxicillin for treatment of persons with anthrax infection may lead to drug resistance to this class of antibiotics during therapy due to the production of beta-lactamases by this strain of *B. anthracis*. They have concluded that the likelihood of inducing penicillin resistance is significantly higher in infections where high concentrations of organisms are present. Therefore, **they do not recommend monotherapy with penicillin.**

   - Rifampin, vancomycin, imipenem, chloramphenicol, penicillin, ampicillin, clindamycin, and clarithromycin are listed by the CDC as possible additional agents to use with either ciprofloxacin or doxycycline.

- Ciprofloxacin and doxycycline are known to have poor central nervous system penetration, and may not be optimal therapy for anthrax meningitis.

3. Washington Hospital Center in Washington, D.C. treated some of the inhalational anthrax patients involved in this outbreak during October 2001. Their infectious disease division developed the following guidelines for the treatment of inhalational anthrax at their institution:

   - Combination therapy with **penicillin 4 million units IV every 4 hours AND ciprofloxacin 400 mg IV every 12 hours**. The rationale being that historically approximately 50% of these cases are associated with meningitis. Penicillin has been well established as a therapy in the setting of bacterial meningitis, whereas experience with ciprofloxacin is still limited. In the event of a penicillin allergy, they recommend the combination of doxycycline AND ciprofloxacin.

   - They recommend the **addition of clindamycin 900 mg IV every 8 hours** (as a third antibiotic) if the patient has signs of mediastinitis, bacteremia, or hemodynamic instability. The rationale is to inhibit toxin production, analogous to the toxic shock syndrome associated with staphylococcal or streptococcal infections.

4. Some experts recommend that corticosteriods be considered for extensive edema or swelling of the head and neck region associated with cutaneous anthrax.

5. Total duration of therapy is 60 days for both cutaneous and inhalational anthrax. Initial intravenous antibiotic therapy can be changed to oral therapy when clinically appropriate to complete the 60-day course of treatment.

6. Limited clinical experience is available and no controlled trials in humans have been performed to validate current treatment recommendations for inhalational anthrax.

References:

1. Johns Hopkins University Center for Civilian Biodefense Strategies. *http://www/hopkins-biodefense.org/*

2. CDC. "Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax." *MMWR* 2001; 50:941-948.

3. CDC. "Update: Investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy." *MMWR* 2001; 50:909-919.

4. Inglesby TV, Henderson DA, Bartlett JG, et al. "Anthrax as a biological weapon: medical and public health management." *JAMA* 1999; 281: 1735-45.

Sincerely,

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